

USAID DIV AutoSyP Final Report

Award-AID-OAA-F-14-00008 "Low Cost Mechanical Syringe Pump to Regulate IV-Fluid Delivery in Low-Resource Settings"

Executive Summary

Objectives and Activities

AutoSyP is a low-cost, low-power syringe pump for controlled fluid delivery in low-resource settings. The key objectives for this DIV Phase I project were to conduct a clinical evaluation of AutoSyP, design and test pilot AutoSyP training programs, and work with potential stakeholders to further implementation and scale-up. In benchtop tests in Houston, we evaluated AutoSyP's mean flow rate accuracy in a controlled setting. During the first visit to Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi we collected feedback from doctors, nurses, and registrars on the user interface of the device as well as the pilot training programs. Nurses from the pediatric wards also attended pilot training programs and post-test evaluations.

After the initial visit to QECH, we made the suggested modifications to our user interface and training program. We also continued benchtop testing to increase accuracy for slow flow rates and occlusion detection. A second site visit occurred in the spring of 2015 to conduct a healthy adult volunteer trial and a pediatric clinical evaluation. We evaluated AutoSyPs performance on 10 healthy volunteers and 30 pediatric patients with flow rates ranging from 5 to 60mL/hour. During this visit, we also talked to potential stakeholders at QECH and Malawi's Ministry of Health (MOH) regarding plans for scale-up into district hospitals. Finally, we spoke with potential manufacturing partners regarding AutoSyP commercialization and developed a Product Requirement Specification document for the device.

Results and Lessons

Results from our feedback sessions showed that majority of the pediatric clinical staff liked the simplified design of the device. They stated that it was easier to use than standard commercial pumps and that syringe placement and the button navigation was more intuitive. However, doctors and nurses thought the device was too big and heavy to practically use in the pediatric ward, and suggested to decrease the size of the device. In the healthy adult study, AutoSyP had less than 3% error in the mean flow rate for all infusions. In the pediatric study, all infusions had error below 6% and more than 90% of syringes were delivered at <5% mean flow rate error.

We learned multiple lessons from this project, especially regarding device features and staffing for clinical evaluations. For future clinical trials, we will hire more nurses and technicians for the study to allow for more schedule flexibility and to decrease on-duty shift times. We will also modify AutoSyP to increase durability and decrease size of the device.

Next Steps

We will continue clinical evaluations of AutoSyP in the maternity ward at QECH in July 2015. This study will validate the use of AutoSyP in delivery fluids to a wider clinical adult population. We are also planning a stakeholder conference call which will involve personnel from Rice, QECH, the Malawi MOH, and 3rd Stone Design, a potential manufacturing partner. We will discuss the scale-up plan, including concerns and interests of all stakeholders. The outcome of this call will be a solidified scale-up plan as well as next steps for any/all stakeholders. This summer, we plan to apply for Phase II DIV funding to continue AutoSyP scale-up.

Background

Overview of project including timeframe, funding level (DIV and leverage/cost share) and brief contextual information about the location of implementation and testing.

Rice 360: Institute for Global Health Technologies at Rice University was awarded DIV Phase I funding for the project titled “Neosyp: Low Cost Mechanical Syringe Pump to Regulate IV-Fluid Delivery in Low-Resource Settings.” Principal Investigator Maria Oden led the project, which was implemented from March 2014-June 2015 with the support of \$100,000 in funding from DIV.

The project involved the development and testing of an automatic syringe pump designed for use in low-resource settings. Design refinement and benchtop testing was conducted at Rice University in Houston, TX. User evaluation and clinical evaluation was conducted at Queen Elizabeth Central Hospital in Blantyre, Malawi.

What work had been done before the USAID grant that lead up to this project?

The need for a low-cost, low-power syringe pump was originally presented to Rice 360 researchers by partner clinicians at Queen Elizabeth Central Hospital in 2009. During 2010-2011, Rice University students developed NeoSyP, a completely mechanical syringe pump powered by a constant-force spring. Students performed initial benchtop evaluation and feedback was obtained from partner clinicians. Based on the clinician feedback, the device was updated to be quieter and more robust and to deliver at more customized rates and volumes by a student team during the 2012-2013 academic year. This updated device, called AutoSyP, uses the same constant-force spring mechanism to depress syringes with mechanical energy, but also utilizes a microcontroller to allow for more customized control. From May 2013 through February 2014, student interns and Rice 360 staff furthered the development of the device by decreasing its size, adding a position tracking mechanism, and performing extensive benchtop accuracy testing.

Please explain the causal links between your projects activities and the desired development impacts (the theory of change).

The ultimate goal of this project is to increase global access to safe delivery of life-saving IV drugs and fluids. Increased access to safe infusion of fluids will address neonatal deaths due to pneumonia, tetanus, preterm birth complications, and sepsis, all of which require controlled infusions for management and treatment. As seen in the table below, these four causes of neonatal death account for 57% of the ~2.8 million neonatal deaths that occur each year [1]. Over 99% [2] of these deaths occur in low-resource settings where access to safe syringe and infusion pumps is limited [3]. Thus, we theorize that AutoSyP could ultimately prevent up to ~1.6 million neonatal deaths per year through increased access to safe infusions of drugs and fluids in neonates in the developing world. Additionally, use of AutoSyP would improve the quality of

care and prevent morbidity in neonates who did not previously have access to safe and accurate fluid infusion.

| 2013 Global number of neonatal deaths by cause [1] | | | | | | | | |
|--|------------------------------|-----------------|-----------|---------|----------|----------------|--------------------------|--------------|
| | Pre-term birth complications | Neonatal sepsis | Pneumonia | Tetanus | Diarrhea | Birth asphyxia | Congenital abnormalities | Other causes |
| Number of neonatal deaths by cause | 965102 | 420970 | 135669 | 49446 | 19512 | 661682 | 276483 | 232133 |
| % of neonatal deaths by cause | 34.95% | 15.25% | 4.91% | 1.79% | 0.71% | 23.97% | 10.01% | 8.41% |
| Deaths due to pneumonia, tetanus, preterm birth complications, sepsis | 1,571,187 | | | | | | | |
| % of neonatal deaths due to four conditions | 56.9% | | | | | | | |

Safe infusion of drugs and fluids is critical for many medical applications outside the neonatal population. For example, AutoSyP could be used for drug delivery for the prevention of seizures in pre-eclampsia/eclampsia as well as in effective treatment of cardiovascular disease and in treating cancer. Using AutoSyP to help treat these three conditions alone would impact approximately 10 million more people each year in LMICs [4].

| Number of cases for other AutoSyP applications in LMICs [4] | |
|--|-----------|
| Pre-eclampsia/eclampsia | 2,996,280 |
| Cancer | 4,517,558 |
| Ischaemic Heart Disease | 2,932,092 |

1-2 Paragraph description of organization/company

Our team includes bioengineers from Rice University and clinicians from the University of Malawi College of Medicine/Queen Elizabeth Central Hospital. Since 2007, Rice 360°: Institute for Global Health Technologies has developed and disseminated global health technologies. Three Rice 360°-designed technologies have been scaled up nationally in Ecuador, Swaziland, and Malawi. The PI and Co-PI, Drs. Oden and Richards-Kortum, have more than 20 years of experience in medical device design, and focus on developing and implementing appropriate health technologies for low-resource settings. They have led the development of AutoSyP, including incorporating design refinements, working with the team from Queen Elizabeth Central

Hospital to design training programs, developing a Product Requirements Specification and identify manufacturing partners, and working with the Malawian Ministry of Health to develop a countrywide implementation plan. A Research Engineer, together with the Director of Technology Development at Rice 360, prototyped the device, performed benchtop testing, conducting user interviews, monitoring the device performance during clinical evaluations, and integrated design feedback based on field evaluations.

The Rice team has collaborated with Queen Elizabeth Central Hospital (QECH) since 2007 to design and evaluate a suite of technologies to address challenges to newborn care in Africa. QECH is a tertiary hospital in Blantyre, Malawi. QECH has a high patient volume and the academic foundation to support accurate data collection and protocol adherence, and provides expertise to translate knowledge gained in this study to other hospitals in the region. All clinical research undergoes IRB approval in a well-defined, rigorous process. Drs. Molyneux and Dube at Queen Elizabeth Central Hospital have extensive experience delivering pediatric care in low-resource settings, including in identifying clinical needs and constraints, and in implementing new neonatal and pediatric health technologies. Dr. Molyneux has more than forty years of experience leading a low-resource pediatric ward. Most recently, Dr. Molyneux worked with Rice to implement the clinical trial of the bubble CPAP (bCPAP) device and to train nurses in its use. Drs. Molyneux and Dube are leading physicians and researchers in Malawi and have extensive, long-standing relationships with government officials from the Ministry of Health and other public agencies, and non-governmental organizations, including Save the Children, for example. They led the clinical evaluation of the device, worked with the Rice team to design and assess training programs, and helped develop a country-wide implementation plan.

Mission Statement

Our mission in this project is to develop and validate a syringe pump that is appropriate, affordable, and accessible for low-resource settings. Our first step was to develop and test the syringe pump for neonatal and pediatric populations. However, there are numerous additional uses for a low cost syringe pump that can infuse accurate small volumes of medication including maternity, chemotherapy, and cardiovascular uses. Ultimately, we aim for the sustainable dissemination of this syringe pump to reduce mortality in the developing world. We have chosen to focus initially on the neonatal population which is particularly vulnerable.

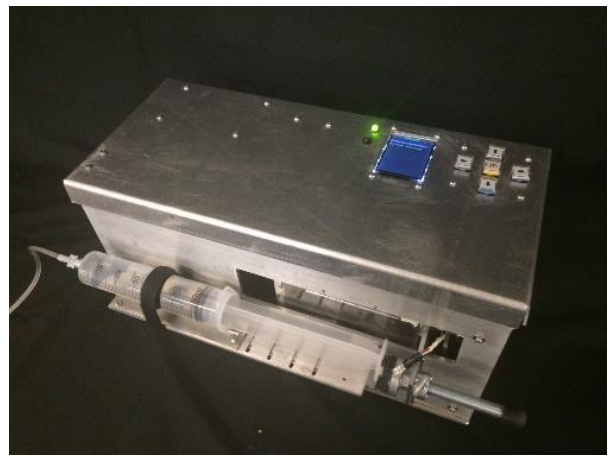
More broadly, our Rice 360-QECH partnership focuses on developing and implementing low-cost technologies that can address the major causes of death and disease in low-resource settings.

Program Design & Implementation

Device Overview

The AutoSyP device is designed to be low-cost, robust, and have low power consumption. It is operated in a similar manner to commercial syringe pumps. First, a syringe is loaded on the syringe pump. The user has the option to enter the syringe brand, syringe size, infusion rate,

and total infusion volume. During the infusion, the infusion screen displays the volume dispensed, time remaining, and set infusion rate. The user has the option to pause the infusion and can adjust the infusion settings or quit the infusion. Visual and audio alarms on the device indicate a pressure occlusion, low accuracy, empty syringe, low battery or a mechanical malfunction.



AutoSyP Syringe Pump

The device's microcontroller automatically controls the rate of fluid delivery. To conserve electrical energy, a spring within the device helps provides energy to depress the syringe, replacing a portion of the electrical energy that is normally used to depress the syringe. The rate of energy release from the spring is controlled by the microcontroller and a motor within the device. This spring is wound manually by the user in between uses by simply pulling the depressor to the left edge of the device. Because of this, the device can run on battery power for 20 hours, a highly beneficial feature for low-resource settings where the power supply may be unreliable. AutoSyP can also run off the wall power supply when it is available; when plugged into the wall, the battery is recharged. The device is designed for generic syringes of size 5, 10, 20, 30 and 60 ml with flow rates up to 60 ml/hr, so consumable costs are minimal.

[What were the goals/targets of the project?](#)

The goals of this project were divided into four aims:

Aim 1: Conduct a clinical evaluation of AutoSyP to assess the potential impact of the device to improve treatment for neonates and pediatric patients who require parenteral fluid and/or IV medication.

Aim 2: Design and pilot test training programs to enable use of the AutoSyP in district hospitals.

Aim 3: Working with potential commercial partners, we will engineer AutoSyP for commercial manufacture.

Aim 4: In partnership with the Malawian MOH, convene a stakeholders' meeting to develop a sustainable, country-wide implementation plan to deploy AutoSyP at district hospitals in Malawi.

[Describe the implementation of this project.](#)

Benchtop Testing & Design Refinement

In Houston from March-October 2014, the Rice team focused on extensive benchtop testing of the accuracy of the device as well as device design refinements. The benchtop testing included calibration of the device flow rates and position tracker as well as benchtop accuracy testing according to relevant international standards (IEC 60601-2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers).

The focus of the device design refinements was an update of the user interface (UI). After extensive conversations with QECH clinicians on the most important clinical parameters to be programmed when using the pump (e.g., flow rate, total infusion time). We then consulted with an expert in human factors to update our UI to incorporate all relevant parameters. The new UI design includes a larger screen and more intuitive buttons for programming the device (details in Appendix A). It allows for the main programming functions of the device to be easily accessed and is designed to reduce user error.

Additionally, a pressure sensor was added to the device in order to track the pressure in the IV line during an infusion and monitor for occlusions. This setup was tested and calibrated in a benchtop setting after discussions with clinicians on the desired functionality of an occlusion alarm and benchmarking with occlusion alarms on commercial devices.

Clinical Evaluation Preparations

Before the initial training evaluation in Malawi, the Rice-QECH team generated training materials for AutoSyP, including a user manual, two job aids, a post-test, and a training agenda. These materials were designed based on our bCPAP training program which trained a similar population of nurses in central and district hospitals in Malawi.

In preparation for the clinical evaluations, the Rice-QECH team also submitted research protocols for the clinical evaluation of AutoSyP to Rice University Institutional Review Board (IRB) and the National Health Sciences Research Committee (NHSRC) in Malawi and obtained approval for the planned evaluations.

Initial In-Country Evaluation and Feedback

In November 2014, the AutoSyP Research Engineer traveled to Malawi to work with QECH partner physicians to conduct initial training sessions on the use of the AutoSyP device and gather feedback from potential users on the device. Feedback was obtained from nurses, registrars, and doctors in the pediatric and maternity wards at QECH as well as nurses from the Kamuzu College of Nursing. The device was presented to 10 doctors and 3 registrars from the pediatric wards, 10 doctors and 2 registrars from the maternity ward, and 5 professors at the nursing college. An additional 12 nurses also went through our pilot training program in order to receive appropriate feedback on the AutoSyP training materials.

Based on the initial in-country evaluations, we further updated the device UI in preparation for the clinical evaluations. In particular, the pause screen had too many options to select and unclear direction on what buttons to press. Thus, the pause screen was edited to have fewer options and more instruction on what buttons to press. Also, color-coding was added to the programming screen, such that a programmed value changed color once it was selected by the user.

After the initial training, all nurses provided feedback on their training experience. The nurses requested more clinical instructions for setting up and monitoring cannula sites, as well as

practice and training on loading the syringe and priming the IV line. Nurses were also confused about navigating through setup screens and thought that the user manual and job aids did not have sufficient background on what buttons to press to move up and down between levels or modes. The nurses would prefer more practice time with the device to become more comfortable with it. Based on this feedback, the training schedule and materials were updated. More clinical background and demonstrations were added to the training schedule, as well as practice time and practical evaluations for the clinical preparations (e.g., priming the line, inserting the cannula). The user manual and job aids were updated to include more pictures of the UI including the corresponding buttons to press while navigating through the UI. A separate clinical user manual, an additional clinical job aid, and an IV preparation check list were generated to include thorough instructions on the clinical preparations for AutoSyP use. The post-test was also updated to include evaluation of clinical aspects.

Clinical Evaluations

Evaluations of the clinical accuracy and usability of the device were carried out in February and March 2015. In Phase I, 10 healthy adult volunteers were enrolled and were administered normal saline at flow rates that would be similar to those received by neonatal and pediatric patients. This initial study was aimed to validate the safety and accuracy of the device in a healthy, low-risk population.

Phase II of the study was intended to evaluate the accuracy and usability of AutoSyP in its intended clinical setting with the target patient population. In this phase, we enrolled 30 babies in the pediatric department at QECH who had been prescribed IV fluid infusions. Three nurses were trained on AutoSyP use, clinical preparations, and study protocol and recruitment procedure. These nurses managed patient recruitment and consent, set up the device, IV line, and cannula during the study, and closely monitored the device and baby for any infusion-related complications. In addition, four trained technicians monitored the technical performance of the AutoSyP device and intervened if there were any technical complications.

Manufacturing and Implementation Planning

Throughout the grant period, the Rice-QECH team also focused on planning the future scale-up and sustainable implementation of the AutoSyP device. In preparation for commercial manufacturing, we generated a Product Requirement Specification (PRS) that detailed the technical specifications required for the AutoSyP device (Appendix B). We also met with potential manufacturing partners to gauge interest in future partnerships and gather feedback on the device.

We also held several meetings to engage other stakeholders and discuss sustainable scale-up. Most importantly, the Rice team met with our partner program manager at the Malawi Ministry of Health to discuss AutoSyP's scale-up throughout Malawi and the ways it will both emulate and improve upon the strategies employed for bCPAP countrywide scale-up in Malawi. Although we did not yet have the opportunity to meet with district hospital officials directly regarding AutoSyP scale-up, our bCPAP implementation team has close relationships with the Malawian district hospitals and will be able to facilitate partnerships in the future. We also had the opportunity to

discuss the AutoSyP project with Save the Children, a potential implementation partner. As mentioned above, we also met with nurses, doctors, nursing professors, and manufacturers to help clarify interest and generate strategies for scale-up.

[What organizations or stakeholders did you engage to implement the project? Please describe those relationships.](#)

The most important collaboration for this project is between the Rice-QECH leadership team. The Rice team began its partnership with QECH pediatrics in 2007, with the goal of designing and evaluating a suite of technologies to address challenges to newborn care in Africa. Together we have developed a low-cost set of LED-based phototherapy lights to treat jaundice, which have been in use at QECH since 2008. We worked together since 2009 to develop and test a low-cost bCPAP device to treat neonatal respiratory distress. Under the leadership of Dr. Molyneux, the bCPAP device underwent a clinical evaluation at QECH and is currently being scaled up throughout the country.

Also at QECH, we regularly engage with the entire pediatric clinical staff, including consulting physicians, registrars, clinical officers, nurses, as well as nursing professors and students at the neighboring Kamuzu College of Nursing. They have been instrumental in the implementation of bCPAP and phototherapy lights, as well as early-stage evaluations of other neonatal health technologies. Buy-in and feedback from these groups is critical to the success of the AutoSyP clinical evaluation and long-term implementation. The clinical staff provided valuable feedback on the AutoSyP device and training programs. Three nurses underwent extensive training and managed the clinical evaluation, and were thus also able to provide more in-depth feedback on the use of the device.

The Malawi Ministry of Health (MOH) is another critical partner for scale-up. During country-wide scale-up of the bCPAP program, we worked with the MOH to incorporate bCPAP training and data collection into the existing operations of the national health system. Key ministry officials are heavily invested in this partnership and are excited for the opportunity for future collaborations and scale-up of promising devices in neonatal care. To that end, we began planning for AutoSyP scale-up with program officer Norman Lufesi, with the goal of loosely following our previously successful the model of bCPAP scale-up while refining the procedure from lessons learned.

The University of Malawi Polytechnic Institute is adjacent to QECH and is Malawi's leading technical and engineering school. With support from the Lemelson Foundation, Rice University is partnering with the Polytechnic to help start a biomedical engineering program and build an innovative prototyping space for Polytechnic students to utilize. The aim of this project is to foster biomedical device training and innovation in Malawi and facilitate local expertise in the design, manufacture, and maintenance of life-saving medical equipment. Two Polytechnic staff were trained in the use and maintenance of the AutoSyP device and helped managed the technical aspects of the clinical evaluation. Moving forward, we plan to further engage the Polytechnic staff and students in order to explore local manufacturing and maintenance training

for the AutoSyP device.

We also engaged potential manufacturing partners for this project. 3rd Stone Design is a design firm based in San Rafael, California. Rice and 3rd Stone Design collaborated to design and manufacture a dosing clip for an oral syringe to ensure accurate dosing of liquid medications. 3rd Stone Design licensed the technology from Rice and produced 213,000 clips for the 12,000 participants in Swaziland's national program to prevent mother-to-child transmission of HIV. The clips are being disseminated in partnership with the Clinton Health Access Initiative and the Swaziland Ministry of Health. 3rd Stone Design worked with the Rice-QECH team to refine the bCPAP device for commercial manufacture, produced all units for clinical-evaluation and countrywide scale-up, and has recently licensed the device from Rice. 3rd Stone Design also recently obtained CE Mark for the bCPAP device. For the AutoSyP project, we have had initial discussions with 3rd Stone Design on forming a manufacturing partnership similar to that of bCPAP. We have also received initial feedback from 3rd Stone Design CEO Robert Miros on design for manufacturing.

Rice 360 also has a relationship with Becton Dickenson (BD) Global Health. The goal of BD's Global Health Initiative is to help strengthen healthcare systems and increase access to healthcare in the developing world, through methods that include investing in new technologies [5]. Since 2013, BD and Rice have participated in collaborative design reviews for Rice's global health technologies, with BD providing design and commercialization advice and evaluating the potential of future manufacturing partnerships for these devices. We have presented the AutoSyP project to BD on multiple occasions and have gained feedback on design as well as on syringe pump regulatory procedures.

Rice 360 also met with Save the Children to discuss potential partnerships for scale-up of technologies. Save the Children is an international NGO that aims to protect and nurture children throughout the world, and has a longstanding history of working to reduce maternal and child mortality in Malawi. In collaboration with other funders, Save the Children has established the Saving Newborn Lives Initiative, a program that emphasizes provision of Kangaroo Care and newborn resuscitation at district hospitals. We met with officials from this program to present AutoSyP and explore the possibility of future collaborations in training and implementation in district hospitals in Malawi.

[What were the demographics of the beneficiaries \(or customers, if this is a private sector project\)? How did you determine who participated / benefited?](#)

The primary beneficiaries for this project are the pediatric patients and their families at QECH. QECH is a tertiary care facility and treats patients from various regions in Malawi. The study was conducted in the Chathinka Neonatal Intensive Care Ward, the Pediatric Nursery High Dependency Unit, and the Pediatric Special Care Ward. Patients were eligible to participate in the study if they were prescribed an IV infusion by their clinician, their parents consented to participation, and an AutoSyP device was available at the time of starting a new infusion on the baby. Participants ranged in age from birth to 1 year. If an AutoSyP device was not available or

the patient's parents did not consent, the baby was treated with the ward's standard of care for IV infusions. Participants in the initial study benefited from safe, controlled infusions as well as from additional nurse monitoring by the study nurses. If the AutoSyP device is implemented permanently and broadly, all patients receiving IV fluids would benefit from the availability of safe and controlled infusions.

The secondary beneficiaries for this project are hospital nurses. Nurses will benefit from the project because they will have a safe, reliable, and accurate method for providing infusions to patients. This will improve the overall ward workflow and allow nurses to focus more attention on other critical care tasks.

What challenges arose during program implementation, and how were they addressed?

It was not originally foreseen that a redesign of the user interface would be necessary to address the needs of the end user and ensure safe use of the device. This UI design update required significant time and effort and consequently pushed back our timeline for clinical validation. However, we were permitted by DIV to make some small adjustments to milestone deadlines and update the UI as required. Ultimately, we were still able to complete the device study within the grant period.

During the clinical evaluation in the pediatric ward, we recognized factors in the environment that could contribute to device wear and thus impact the long-term durability of the device. For example, we suspected that the humidity in the ward might cause some sensors in the device to report erroneous values, and that rough handling can cause internal wires to become dislodged. We addressed these issues in two manners – one for the short-term study and one for long-term implementation. For the short-term study, we performed preventive maintenance checks on the device before each infusion. We also incorporated an hourly maintenance check that took place throughout each infusion. In this way, we could catch any potential problems immediately. For the long term, when constant technical monitoring will not be feasible, we realized that a more robust device design is necessary. To that end, we have made a priority next step be to work with an industrial design expert to refine the design of some aspects of the device for ease of manufacture and long-term durability.

Another unforeseen obstacle was the lack of availability of luer-lock IV tubing for use with luer-lock syringes. QECH is only supplied with generic IV tubing that is intended to attach to an IV bag. With the few available syringe pumps at QECH, nurses would typically cut the end of this tubing and slide it onto the syringe. However, this creates an unstable connection that is sensitive to pressure buildup in the line. Our short-term solution was to bring luer-lock compatible IV lines from the US for the clinical evaluations. In the long term, we will look to find locally available luer lock connectors or to design a more secure method for attaching a generic IV line to a syringe. This issue is not unique to the AutoSyP syringe pump – all syringe pumps require tubing that is distinct from generic IV bag tubing. Often, commercial infusion pumps require a specific proprietary tubing set to function properly. In contrast, AutoSyP works with any brand of extension set tubing as long as it is luer-lock.

For implementation, we hired two pediatric nurses from QECH who were not on duty during the month of the study. This decreased the work load of the nurse during the study, and they could fully devote their time to patient recruitment and monitoring. However, most nurses off duty were also assigned to other pediatric trainings at QECH and at other districts. A few times during the study both nurses were busy with other trainings. We had to hire and train a third nurse half way through the study as an additional substitute for both nurses. For future studies, three or four nurses will be hired to mitigate these issues.

Evaluation Design

How did you verify whether or not you met project goals and objectives? What indicators and instruments were used to measure them?

User Feedback

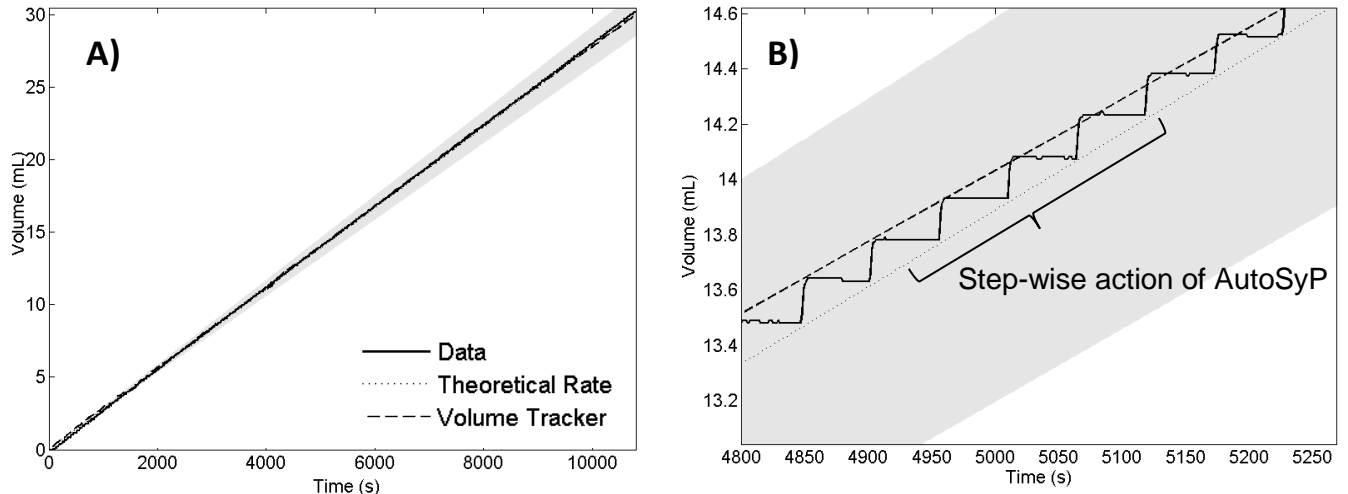
To collect user feedback, there were two feedback sessions that occurred during the year. The first session was conducted in the fall with doctors, registrars, and nurses in the pediatric and maternity wards. This session mainly focused on the training program and the design of the user interface. Pilot training sessions were also completed in the fall to determine the impact of our training program for AutoSyp. Twelve nurses went through the training program and four nurses completed a post-training evaluation. The evaluation tested nurses on preparing a syringe for an infusion, programming the infusion, and special case scenarios during an infusion. Our goal for the training program was to have all nurses score above 80% on the post-training evaluation.

After initial feedback and training sessions, we modified the device and training program for clinical evaluations in the spring. Once we completed clinical testing, feedback surveys were given to nurses and technicians in the study. This feedback session mainly focused on how the device functioned in the wards during the study and device modifications that would make it easier to use in the wards.

Clinical Performance

In order to measure the accuracy of AutoSyP, the device used a volume tracker to determine how much volume was dispensed over a period of time. Data points would be displayed every time the device dispensed fluid in order to collect multiple data points and determine the actual flow rate. These data points were collected on a laptop from the Arduino Mega board in the device. We used the data collected to calculate the mean flow rate accuracy for each infusion. Using this method, we were about to quickly determine if the device was infusing solution at the programmed flow rate. During benchtop testing, we compared values from the volume tracker with the mass data collected to confirm accuracy of the device. However, during clinical trials, we were not able to measure the mass of the fluid dispensed and only relied on volume tracker data to determine mean flow rate. The figure below is an example of benchtop data taken.

Our goal was to have all infusions be within 5% of the programmed flow rate. We also tracked performance of the pressure occlusion alarm by recording each time a true occlusion occurred in the patient line and recording each time the AutoSyP device alarmed for an occlusion, and comparing the two occurrences.



A) Example benchtop accuracy test data. **B)** Zoomed in view of benchtop accuracy data. The solid line represents volume delivered based on the mass data and the dashed line represents the volume delivered based on AutoSyP's internal volume delivery tracking mechanism. The dotted line represents the theoretical rate and the gray area is the $\pm 5\%$ error range.

For impact evaluations: What was the evaluation design? Please include if applicable: key study questions, randomization design, sampling strategy, power calculations, qualitative methods used, etc.

User Feedback

Initial feedback for the AutoSyP device was taken from nurses, registrars, and doctors in the pediatric and maternity wards at Queen Elizabeth Central Hospital (QECH) as well as nurses from the Kamuzu College of Nursing. The device was presented to 10 doctors and 3 registrars from the pediatric wards, 10 doctors and 2 registrars from the maternity ward, and 5 professors at the nursing college. An additional 12 nurses also went through our pilot training program in order to receive appropriate feedback on the AutoSyP training materials. For the pilot program, nurses were trained on how to set up and program the device for an infusion protocol. The nurses were given time to practice setting up the device for infusion. Once they had successfully programmed the device for an infusion, we discussed the ease of use of the user interface, the overall infusion setup, and the device. We also asked the nurses what they liked about the device and if they had any modification suggestions for the device.

A second feedback session was taken in the spring once clinical evaluations were completed. Both nurses and technicians were given feedback surveys about the device and study. The following questions were asked on each survey:

- In what situations will it be helpful to use this device?

- What about the device did you find confusing or difficult to operate?
- What features would you like the device to have that it does not currently have?
- Were the protocol setup screens easy to follow and have all information needed to start an infusion?
- What are your questions or concerns about the device?

Clinical Performance

In order to determine the accuracy of the device, the mean flow rate calculation from the ISO standard (ISO 28620-*Medical devices - Non-electrically driven portable infusion devices*) was used to determine the mean flow rate of the device. The standard requires a 15% accuracy, however for the neonatal and pediatric populations we feel it is important to have a higher accuracy. Our goal for all initial benchtop testing and clinical trial infusions was to have the mean flow rate within 5% of the programmed flow rate. According to the standard, the mean flow rate, Q_m , was determined by measuring the time, T , necessary for the device to deliver the majority of the nominal volume, V_n , of solution. This volume can be determined by the weight of the solution delivered divided by its density. This was calculated using the equation $Q_m = (0.75 * V_n)/T$.

Summarize preliminary (or final) quantitative and/or qualitative results of the intervention.

User Feedback

Positive Feedback

Nurses involved with the pilot study liked the simplified design of the device and stated that it was easier to use than standard commercial pumps. Other commercially available pumps have too many components and buttons that make it difficult to use in the wards. On the AutoSyP device, the syringe placement and the button navigation was also easy to figure out. 5 of the pediatric nurses also agreed that it was easy to use and 5 doctors state that the UI design was more simplified than other pumps. The technicians and nurses in the pediatric ward thought the occlusion alarm was safer and more sensitive than commercial pumps.

The nurses liked that the device had a rechargeable battery and does not always depend on access to wall power. In most wards at QECH, the power supply is consistent, but some of the outlets do not work and would need to use battery power to run the device. District hospitals would also need battery power since the power supply is inconsistent in these areas. Compared to the other syringe pumps in the pediatric nursery, the nurses thought AutoSyP was more durable and robust. The nurses would like to see the device be smaller or less bulky since most of the wards have limited space. 2 technicians, 7 nurses, 5 doctors and 1 medical student gave feedback on the device.

A summary of responses are listed in the table below:

| What features do you like about the device? | Technician (2) | Nurses (7) | Doctors (5) | Med student (1) | Total (15) |
|---|----------------|------------|-------------|-----------------|------------|
| Backup battery power | 100% | 71% | 100% | 100% | 87% |
| Occlusion alarm | 100% | 100% | | | 60% |
| Device durability | | | 100% | 100% | 40% |
| Simple button navigation | | 29% | 60% | | 33% |
| Simplified design and easy to use | | 29% | | | 13% |
| Priming and preparation reminders | | 14% | | | 6% |

Suggested Device Modifications

Majority of the doctors and nurses agreed that the device was too big and heavy to practically use in the pediatric ward. A major modification suggestion was to decrease the size of the device. Nurses using the device also stated that the text on the UI LED screen was too small and hard to read. The text would need to be bigger to avoid any programming errors. Nurses also had difficulty pushing the device arm all the way back to prepare the device for the infusion. Two technicians, 7 nurses, and 5 doctors suggested modifications for the device. A summary of responses are listed in the table below:

| What are your suggestions or modifications to the device? | Technicians (2) | Nurses (7) | Doctors (5) | Total (12) |
|---|-----------------|------------|-------------|------------|
| Decrease the size/weight of device | | 100% | 40% | 64% |
| Increase the size of text on UI screen | | 29% | 20% | 21% |
| Add LED light when alarm goes off | | | 60% | 21% |
| Secure pressure sensor on device | 100% | 14% | | 21% |
| Include a more ergonomic way to push back device arm | | 29% | | 14% |
| Run at flow rates of 90-120ml/hr | | | 40% | 14% |
| Refine occlusion alarm sensitivity | 100% | | | 14% |
| Add a visible pause button | | 14% | | 7% |

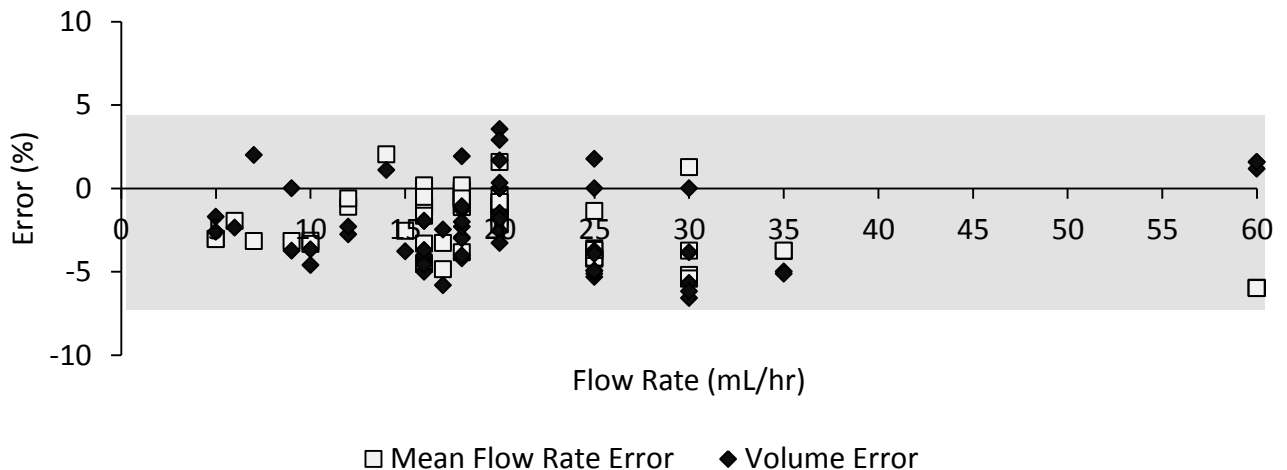
Clinical Performance

The clinical evaluation was divided into two phases in order to test the accuracy of the device and the functionality of AutoSyP in the pediatric wards at QECH. In Phase 1, we enrolled healthy adult volunteers to receive normal saline at flow rates that would be similar to those received by neonatal and pediatric patients. Our goal was to evaluate the system at flow rates and volumes that were similar to those that were expected for children, but to do it initially with 10 infusions in healthy adults. We saw less than 3% error in the mean flow rate for all 10

patients. Below is a listing of the results for 10 trials in healthy adults. There were no true occlusions or occlusion alarms in the adult trials.

| Trial # | Flow Rate (ml/hr) | Syringe Size (ml) | Total Volume (ml) | Mean Flow Rate Error (%) |
|---------|-------------------|-------------------|-------------------|--------------------------|
| 1 | 20 | 20 | 20 | -0.41 |
| 2 | 3 | 10 | 9 | 1.05 |
| 3 | 15 | 60 | 120 | -2.65 |
| 4 | 15 | 60 | 120 | -2.90 |
| 5 | 5 | 10 | 10 | -1.04 |
| 6 | 10 | 60 | 60 | -1.30 |
| 7 | 20 | 20 | 20 | -1.21 |
| 8 | 5 | 10 | 10 | 0.71 |
| 9 | 60 | 10 | 60 | -0.80 |
| 10 | 3 | 10 | 10 | 2.51 |

In Phase 2, we enrolled 30 pediatric patients from the Chathinka Neonatal Intensive Care Ward, the Pediatric Nursery High Dependency Unit, and the Pediatric Special Care Ward and completed 59 infusions. For this trial babies were given one or more of the following: normal saline, Ringer's Lactate, dextrose, and KCL. Flow rates varied between 5 ml/hr and 60 ml/hr. Volume delivered varied between 8 ml and 95 ml. Syringe sizes were all 60 ml. These values were based on physician choice and the need for the prescribed infusion. The mean flow rate error and mean volume error was calculated after each infusion. Overall, all infusions had error below 6% and more than 90% of syringes were delivered at <5% error for both mean flow rate and volume error.



Mean flow rate error and mean volume error as a function of flow rate for each syringe of fluid delivered. 30 pediatric patients were tested with flow rates ranging from 5mL/hr to 60mL/hr. More than 90% of syringes were delivered at <5% error for both mean flow rate and volume error.

The ISO 28620 standard for non-electrically driven portable infusion devices requires mean flow rate be within 15% of expected flow rate set by the user, which we met in all subjects. The errors from exact fluid delivery are well within the aforementioned standard, but we believe that our system can perform more accurately with some additional modifications. We hope improve our accuracy through refined calibration such that we have <5% mean flow rate error in all cases.

In addition to monitoring the mean flow rate, we also monitored the occlusion alarm on the device. We had 59 instances where the IV line occluded and stopped fluid delivery temporarily until a nurse could fix the occlusion. Due to the small nature of the children, this is a very common occurrence in any neonatal IV therapy. We were able to determine that the occlusion alarm alerted the nurse every time a true occlusion occurred. There were 17 false occlusion alarms on AutoSyP over 230 total hours of infusions. We are currently evaluating whether the AutoSyP occlusion alarm is too sensitive, and whether we should modify our system to allow slightly more increase in pressure before indicating that an occlusion has occurred.

[Did anything occur during implementation or data collection that could have threatened data quality?](#)

In later infusions in Phase 2, we noticed inaccuracies in the embedded sensor to detect flow rate and volume delivered. The sensor was not tracking the complete distance traveled by the device and was under-reporting the total volume dispensed. Due to these inaccuracies, the mean flow rate calculations were also affected and lower than expected. It should be emphasized that the inaccuracy was only in our position tracking sensor and not in the actual fluid delivery of the device. In benchtop testing, flow rate accuracy can be continually monitored by weighing the fluid that is dispensed from the syringe. However, in clinical evaluations, this is not possible, so a position tracking sensor was used as a proxy for flow rate measurements. Once the sensor error started occurring, the true accuracy performance of the pump was verified manually by visually tracking the volume in the syringe at set intervals. We also conducted benchtop tests to confirm the discrepancy between the volume tracker and the true flow rate. These tests confirmed that the device was accurate to the programmed flow rate, but the volume tracker was under-reporting volume dispensed. We are working on improving or changing the sensor so that we can be more confident in its reported results. In its current state, the maximum measured deviation from exact volume dispensed is 5.36% due to sensor error.

There were 6 instances out of a total of 59 infusions where the nurse did not properly set up the syringe pump settings for the infusion. In five instances, the nurse programmed the wrong flow rate, syringe size, or total volume due to incorrect use of the button navigation system. These mistakes were detected by the researcher on duty and corrected by adjusting the settings before the start of the infusion. The final instance was associated with not pulling the device arm back far enough to ensure that the entire syringe was dispensed. All of these situations were corrected before the start of the infusion to successfully deliver all fluid to the patient at the prescribed flow rate. We are evaluating changes in training and programming interface to

reduce possible system setup mistakes.

Are there any methodological limitations to the analysis?

As explained above, the position tracking inaccuracy introduced small methodological limitations to the analysis.

If you have significant new or different evaluation plans for your future work, please describe.

We are currently analyzing our original volume tracker and looking to change this part of the device to be more durable in low-resource settings. From our Phase 2 results, we observed that the reported results were under reporting the volume dispensed from AutoSyP. A new and more durable volume tracker will allow us to accurately monitor the amount of volume infused and improve our analysis of the device. We will also be manually monitoring the volume in the syringe over the course of all infusions. Having both of these data points will allow us to quickly determine the status of the device during each infusion.

Findings

What lessons were learned during implementation? What are these lessons based on? If applicable, please provide details about lessons in the following areas, especially those that could inform future scale up or replication:

Staffing patterns/skill sets required for implementation

For implementation, we had two pediatric nurses from QECH, two technicians from University of Malawi Polytechnic Institute, and one researcher from Rice University for the entire course of the study. The two nurses were not on duty for their regular nursing shifts during the month of the study in order to solely devote their time for trial recruitment and patient monitoring. This was key for patient monitoring and recruitment, because the nurses did not have other responsibilities or duties during an infusion. One nurse would take the day shift (8am-4pm) for the weekday and weekends and the other would take the night shift (4pm-8am) during the weekdays. The nurses would switch shifts each week depending on availability. A third or fourth nurse would have been helpful for the study as most of the off duty nurses were also assigned to receive other trainings. A few times during the study a third nurse had to be trained as a substitute because both nurses were busy with other trainings.

Two technicians from The University of Malawi Polytechnic Institute were also hired to help the researcher with night shift monitoring. The Rice researcher was in charge of all day shifts (6am-6pm) and one technician was in charge of the night shift (6pm-6am) on weekdays. Both technicians were trained how to setup the device, monitor AutoSyP data, and do minor troubleshooting. If a major problem occurred during night shift testing, the Rice researcher would be called for troubleshooting assistance. A third technician would have been helpful to decrease the number of nights a technician was on duty.

Key partnerships to obtain and/or maintain

As explained above, QECH physicians and nurses, as well as University of Malawi Polytechnic Institute staff, were critical partners for our initial user and clinical evaluations. We will continue to maintain and develop these partnerships as we begin to scale up. We will continue working with QECH staff as we begin our next clinical evaluation in the maternity ward, and we also plan to employ the nurses we've already trained to help train nurses in future district hospitals. Moving forward, we plan to further engage the Polytechnic staff and students in order to explore local manufacturing and maintenance training for the AutoSyP device. We recognized the importance of having at least one full-time engineer working in the hospital during the clinical evaluations, and thus for scale-up and long term implementation, engineering support will also be necessary. We believe that the Polytechnic staff will be a critical biomedical engineering resource to help AutoSyP and other medical devices succeed in scale-up in Malawi.

Additionally, while the involvement of the Malawi Ministry of Health (MOH) only had a minor role in the initial evaluations, it will play a key role in the scale-up. We recognized that establishing and maintaining relationships with the MOH early on in the process can help facilitate the transition to scale-up period.

Contextual information such as cultural/social norms

We conducted testing during weekdays and weekends in order to recruit enough patients for our study. We noticed that very few patients came to the hospital on Sunday. Through conversations with the nurses and clinical staff, most of them said that majority of people will wait until Monday to visit the hospital for treatment. With these observations, we shortened our testing days to Monday through Saturday.

Policy and legal framework opportunities or challenges to implementation

Originally, we submitted our proposal for initial clinical testing to College of Medicine Research and Ethics Committee (CoMREC). CoMREC deemed that this study was of national interest and needed to be submitted to the National Health Science Research Committee (NHSRC). Thus, significant delays occurred due to not understanding the appropriate regulatory board to submit to beforehand. We have found that it is very helpful to have a staff member on the ground be in constant communication with CoMREC and NHSRC to better understand the submission deadlines, guidelines, and procedures. Ultimately, we received approval for our proposal from the NHSRC.

Product or service delivery modifications

Based on feedback from QECH and observations from our clinical trials, we are making changes to the current device design and planning major modifications for next version of the AutoSyP prototype. On the current prototype, we will be increasing the durability of the volume tracker and wire connections inside the device. We are looking into alternative methods to accurately track the volume dispensed by device. This method would be similar to the current system, but be more durable to handle low-resource setting conditions. We are also looking to add a more secure connections for the pressure pad wires as those came loose multiple times during the setup of the device and during travel. We are also planning to simplify the user

interface and increase the text size to make it easier for nurses to correctly program an infusion protocol.

For the next prototype of AutoSyP, we will be making bigger modifications to improve the manufacturability of the device. Instead of using our current pressure pad, we are going to evaluate using a strain gauge to monitor pressure in the syringe and detect occlusions. This will eliminate any wires outside the device and increase durability of the occlusion alarm. We are also changing the case of the device to look closer to a manufactured model. We plan to consult with 3rd Stone Design on the casing and other areas of the device that should be modified for manufacturability. These long term changes will help increase durability of the device in the wards.

[What do the lessons learned from this project imply for future funders and/or policy makers?](#)

From our perspective, lessons learned thus far have been specific to our project, but we would welcome a discussion with DIV about how these lessons might be more generally applicable and how to best communicate any lessons described in this report to relevant parties.

[To what degree and in what contexts can these results be generalized?](#)



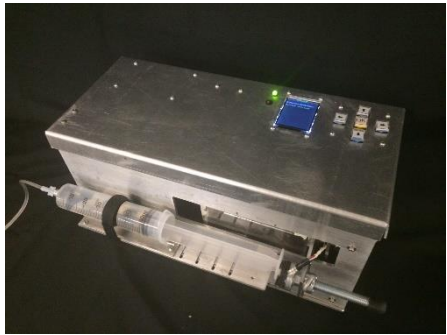
From our results, we can conclude that our device will deliver a variety of drugs and solutions safely and accurately to pediatric patients. Our syringe pump was used for a variety of purposes and treatments in the pediatric ward during the clinical trial. The device was able to infuse each solution accurately despite major changes in the solution (e.g., addition of 10% dextrose, a viscous solution). The device could also be used in environments similar to QECH or other low resource settings. Despite lack of power and resources, AutoSyP still functioned like a normal syringe pump. We are completing another clinical evaluation in pre-eclamptic women in the QECH maternity ward. With these results, we can generalize that AutoSyP will have multiple uses in adults as well as pediatric patients.

Cost-effectiveness & Competitive Landscape

[What existing common practices or competing solutions seek to address the same development challenge as your solution in the areas you intend to operate and scale? How does your solution compare? What are the advantages to users/customers \(including cost considerations?\)](#)

AutoSyP is designed to meet several criteria not adequately addressed by existing syringe pump technologies. AutoSyP is designed to be low-cost, accurate, easy to use and maintain, robust, and compatible with all types of syringes and fluid administration sets.

The table below compares the performance characteristics of AutoSyP to commercially available syringe pumps. Electronic syringe pumps, the most common type of syringe pump available, are highly accurate, but they are often too expensive for the developing world, have complex user interfaces that have led to user errors [6], and have shorter battery lives, which may not be suitable in settings where grid power is unreliable.

| Competitive landscape for syringe pumps | | | |
|---|---|--|--|
| | Electronic Syringe Pump | Springfusor Mechanical Pump [7] | AutoSyP |
| Photo |  |  |  |
| Flow Rates | 0.01 ml/hr to 1130 ml/hr | 0.06 ml/hr - 360 ml/hr. Viscosity correction factor for wide range of drugs requires calculation. | 3-60 ml/hour |
| % Flow Rate Error | 2-3% | +/- 3% at 25°C | <6% |
| Requires external power? | After ~6-10 hrs | No | After ~24 hrs |
| Maintenance | 5-7 year working life with performance tests every 2-3 months | Flow rate sensitive to external conditions, e.g. temperature, height of device relative to site of injection, venous/arterial pressure at injection site | Target: 5 years life with preventive maintenance every 6 months |
| Cost | \$1200 to \$3500 \$200/repair | \$45 for 10ml and \$52 for 30ml spring unit FCT price ranges from \$4.40 to \$9.50 | Current cost ~\$500 and works with several types of syringes and tubing |

Springfusor is a fully mechanical infusion device [7]. The device is available for 10 ml and 30 ml syringe sizes and can be used indefinitely on different patients. While Springfusor, with its low initial cost, may seem to meet many of the requirements of low and middle income countries, it has several limitations that present significant barriers to its adoption in these settings. The first disadvantage is a high per-use cost. The Springfusor works only with Braun syringes and requires proprietary disposable Flow Control Tubes (FCT) ranging in cost from \$4.40 to \$9.50 each. New FCT is required for each volume type and rate of infusion. Therefore, if a patient requires prolonged infusion with varying rates of infusion, it is necessary to change the FCTs for every flow rate modification, thereby increasing the cost of use. Additionally, Springfusor has demanding usage methods that require calculation of a correction factor depending on the fluid to be delivered and the environmental conditions. This can be time-consuming in an already time-constrained environment. Furthermore, to ensure accuracy of flow rate, the following conditions must be maintained:

- Infusate temperature has to be maintained at 25°C with every 1°C change affecting the rate by 2.5%.
- Height in relation to the site of injection site should be within 30 cm; every 30cm change can affect the flow rate by 2.4%.
- Venous pressure of 5mm Hg, with every 20 mm Hg increase in blood pressure reducing the flow rate by 2.2%.

Thus, we believe AutoSyP is an optimal balance between the high-tech, high-cost electronic syringe pumps and the mechanically-driven Springfusor device. It requires minimal electric grid access as it can run for 24 hours on battery power. The cost is significantly less than the electronic pumps as well as less than the per-use cost of Springfusor. Although AutoSyP's max flow rate is currently less than the competing devices (60ml/hr vs >300ml/hr), this is simply because the accuracy has not yet been validated at faster flow rates. We do not foresee any technical limitations in achieving max flow rates comparable to those of Springfusor. Additionally, the mean accuracy of AutoSyP is slightly higher than most electronic pumps, and may be higher or lower than the Springfusor depending on environmental conditions. While we do aim to further reduce flow rate error to <5%, our current 6% error is with the required 15% limit for non-electrically driven infusion devices (ISO 28620: Medical devices — Non-electrically driven portable infusion devices) and also meets the accuracy testing requirements for electrically-driven infusion devices (IEC 60601-2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers).

Please assess the extent to which your solution yields (or has the potential to yield) greater impact per dollar than alternate ways of achieving the same development impacts. Provide estimates of impact per dollar for your solution and alternatives if possible.

Although we have not yet we have not yet performed a specific estimate of the impact per dollar verses a traditional commercial syringe pump, as seen in the above table, AutoSyP is lower-cost than traditional pumps, with comparable per-use cost (syringe and tubing costs) and lifetime. In addition its low cost, because it was designed specifically for use in lower-resource

settings, the device is expected to be more user-friendly, appropriate, and robust for that environment. Therefore, we estimate that AutoSyP pumps will be more accessible, be used more often and more effectively than most commercial syringe pumps. We have noted in our work that at times babies and children don't receive any treatment due to the lack of availability of a functioning syringe pump or the lack of a syringe pump that is easy to use. Also, when a syringe pump is not available, nurses often resort to an IV bag drip which carries the risk of over-infusion and inaccurate flow rates.

Although Springfuser has a lower unit cost than AutoSyP (\$45-\$52 vs. \$500), our estimate of per-use cost spread over the lifetime of the devices shows that AutoSyP is significantly more cost-effective because of the high price of Springfuser's disposable flow control tubing. Assuming a 5-year lifetime of each device, 3 infusions per day, and \$1 disposable (tubing and syringe) costs per use of AutoSyP, the per-unit costs are estimated below.

| Comparison of AutoSyP and Springfuser Costs | | |
|---|---------|-------------|
| | AutoSyP | Springfuser |
| Device cost (avg) | \$500 | \$48.5 |
| Disposable cost (avg) | \$1 | \$6.95 |
| Total uses | 5475 | 5475 |
| Total cost | \$5975 | \$38099.75 |
| Cost per use | \$1.09 | \$6.96 |

We have also not yet performed a formal cost-benefit comparison with other global health interventions. However, in contrast to many interventions in neonatal and adult health care, the syringe pump is an extremely versatile tool that is used in numerous health care applications. As noted above, we estimate that scale-up of AutoSyP to treat neonatal complications, pre-eclampsia, cancer, and heart disease alone could impact up to 12 million people in LMICs.

Scaling Plan (Public sector projects only)

[What should be the scaling path of this intervention? How does this differ from the scaling plan proposed at the beginning of implementation?](#)

The proposed scaling path has been generated as a result of our stakeholder meetings, ongoing research, and lessons learned from bCPAP scale-up. AutoSyP scaling will follow the model of the bCPAP device and consists of two main aspects: 1) collaboration with a commercial manufacturer to produce a licensed, fully commercialized product, and 2) country-wide scale-up in Malawi in cooperation with the Malawi MOH. As with bCPAP, these two efforts will be pursued simultaneously and will require external funding.

Ultimately we aim for a fully commercialized, market-viable AutoSyP device that is licensed to a commercial partner. We believe this is an ideal pathway for long-term, sustainable implementation beyond Malawi. A top priority to reach this goal is to refine the device's design

for commercial manufacture; during this design update we will also aim to increase durability and drive down per-unit cost through economies of scale. We will first solidify a partnership on AutoSyP with one of our manufacturing partners interested in AutoSyP (3rd Stone Design or BD). With the manufacturing partner under contract work, we will develop a commercial-grade AutoSyP. We will simultaneously explore permanent licensing options with this manufacturer or others. We will also contact the manufacturer to produce the units for country-wide scale-up.

After the initial pilot trials, we have found that country-wide scale-up is an effective next step in a controlled implementation of a new technology. It allows for the device use to still be tracked and observed, but in less controlled and more realistic long-term settings. In this way, we can iron out any remaining design and training details before the device has been fully commercialized. In a stakeholder meeting with the Malawi MOH, we discussed this scale-up for AutoSyP and how it will follow the lead of bCPAP scale-up, yet adapt based on lessons learned as well. Key outcomes from the meeting regarding scale-up are listed below:

- The bCPAP program provided bCPAP devices and supplies and clinical and technical training to all public central and district hospitals in Malawi. The scale-up was conducted in 3 phases over 3 years, assigning each hospital to a phase. Each phase also included a baseline period where the current respiratory support methods, as well as corresponding outcomes (including mortality), were tracked. The same outcomes were tracked after distribution and training on bCPAP. AutoSyP will roughly follow this 3-phase method, with a few key differences.
 - In bCPAP scale-up, we found that there was great diversity in the physical and human resources between each district hospital. AutoSyP's initial phase will include the 10 highest-performing hospitals from the bCPAP study. This will ensure a smoother start as we ramp up implementation.
 - The MOH is also doing a pilot project with UNICEF, implementing 10 commercial syringe pumps in 10 district hospitals. The MOH recommended that we compare our first phase of AutoSyP scale-up with the UNICEF pilot project. Pending appropriate funding, we will work with the MOH to implement AutoSyP in 10 separate hospitals and track successful infusions, device performance, repair history, and user acceptance. We have determined that the tracking of device functionality will be one of the most important data collection aspects during the scale-up. This is because syringe pumps are notorious for failure and we do not have long-term performance data from the pilot study.
- We believe AutoSyP scale-up in Malawi will benefit greatly from the paths paved during bCPAP scale-up. Each district hospital has worked with the Rice bCPAP team extensively and has gained experience in data collection and project implementation. Additionally, the Rice-QECH team is familiar with the attributes and performance of each district hospital, which can inform decisions and focus during the scale-up.
- Supply chain for disposable medical supplies is a major issue in Malawi. While AutoSyP implementation only requires syringes and tubing, we hope to avoid the challenges of

US procurement of any supplies. We already know that the syringes are available in-country, but we have not yet found an appropriate IV extension set that is available locally. We plan to work with MOH procurement to find a locally available IV extension set that will be secure and compatible with syringes.

- Physical Asset Management (PAM) is the biomedical engineering program for the MOH. We plan to formally involve PAM in our scale-up plan. Specifically, we will train PAM personnel on common problems and maintenance of AutoSyP, and then discuss strategies for local repair and maintenance, including local availability of maintenance parts and tools. PAM personnel throughout the country will be trained so that they can attend to the devices even during the scale-up phase when study personnel are still available. This will ensure a smoother transition to when PAM is fully responsible for maintenance and repair after the scale-up period is complete.

If your project results justify ongoing public investments: Which stakeholders necessary for future scale-up have already been engaged? Who are the stakeholders that are still needed? What, if any, are their commitments? What are the roles each stakeholder could play? What role would the research findings play in influencing each stakeholder's decision making? What is the engagement strategy and timeline?

The key stakeholders necessary for future scale-up are described below, including our current status in engaging with them.

- Malawi Ministry of Health: The role of Malawi MOH is to aid in expanding to central and district hospitals throughout Malawi. Our main partner at the MOH (Norman Lufesi) has already been engaged and has verbally committed to a scale-up partnership regarding AutoSyP. We still need to meet with other key personnel at MOH to ensure a more comprehensive partnership. We will present our study findings from the QECH pilot in order to demonstrate the performance of AutoSyP in a low-resource hospital in Malawi. We plan to meet with more MOH officials regarding scale-up during our visit to Malawi in June. We plan to secure a formal MOU regarding scale-up once we have secured funding.
- Malawian public hospitals: The administrative and clinical staff at the hospitals throughout Malawi will be key partners in the scale-up. Although we have not yet engaged with these stakeholders regarding AutoSyP scale-up, we already have strong relationships with them from the bCPAP project. Their role will be to lead clinical implementation and assist in data collection. Once we have an official plan with the MOH, we will work with the MOH to formally engage district hospitals.
- Physical Asset Management: We have not yet formally engaged with them on the AutoSyP project. Their role will be to help develop and implement a local maintenance and repair plan for AutoSyP, and to begin its implementation during scale-up. Once we have an official plan with the MOH, we will work with the MOH to formally engage PAM.

- **Manufacturing Partner:** We first need to secure a manufacturing partner for the initial tasks of design refinement and the production of evaluation units for the scale-up. Ultimately we will also need to find a manufacturer to official license the technology; ideally this will be the same as the initial partner. We have a couple of initial options for a manufacturing partner.
 - **3rd Stone Design** – We have discussed with 3rd Stone regarding the initial tasks of design refinement and production of evaluation units. There is initial interest but no formal commitment yet. We plan to have a conference call in July with the Rice—QECH team, MOH contacts, and 3rd Stone Design leadership. After this call, and pending funding, we will seek to secure a formal commitment from 3rd Stone.
 - **Becton Dickenson** – We have presented AutoSyP to BD on multiple occasions and have also received feedback on design and regulatory strategies. If we cannot secure a commitment with 3rd Stone Design, we will discuss further with BD.

If your project results do not justify further testing or public investment: What stakeholders would benefit from learning about the results of this project? Please describe plans to disseminate lessons learned from the project. What role would the research findings play in influencing each stakeholder's decision making? What is the engagement strategy and timeline?

We believe our initial results justify further testing and further public investment.

What role can USAID play in scaling this endeavor?

In order to continue scale-up of the AutoSyP project, we need to secure additional public funds before reaching commercial sustainability. We plan to apply for DIV Phase II funding for our proposed country-wide scale-up and correspond manufacturing partnership. We have attached the cost estimates for this scale-up plan.

Financial Results and Scaling Plan (Private sector projects only, please note that public/private hybrids may need to answer questions from both sections)

What were the financial goals for the target market and overall operations? (sales, costs, estimates for break-even requirements, etc.)? Were these goals met? What are the future financial prospects for the company (e.g. sales, costs, break-even requirements)?

Our initial target market estimation for neonatal/pediatric wards in LMICs is provided in the table below. We estimate that the neonatal/pediatric ward of every healthcare delivery center, (primary healthcare center, rural hospital, district hospital or tertiary care center) should be equipped with an average of five AutoSyP devices. This would mean a requirement of ~4 million units to effectively address neonatal mortality in low- and middle-income countries. The long-term implementation of AutoSyP for the treatment of other medical conditions including pre-

eclampsia/eclampsia, cancer, heart disease will require further evaluation and market need estimation.

| Estimated market for NeoSyP in LMICs [8] | |
|---|---|
| Location | Number of devices, assuming five per healthcare delivery site |
| Africa | 311,026 |
| Eastern Mediterranean | 150,092 |
| SEARO | 1,330,344 |
| Western Pacific excl. Australia, NZ, Japan Korea, Singapore | 1,614,362 |
| Americas excl. Canada, USA | 812,296 |
| Total | 4,218,119 |

As we are in the initial stages of development and have not yet solidified our commercial partner, we have yet to establish long-term financial plans or goals. We recognize the need to further solidify these market estimations and develop a financial plan to help determine inform commercialization decisions.

Do you anticipate requiring additional public funds (grants or subsidized loans)?

Yes, we plan to apply for DIV Phase II funding (discussed above).

Which stakeholders necessary for future scale-up/expansion have already been engaged and which are still needed? Have you made progress towards securing debt or equity financing? What further assistance would you need from USAID or another public entity to secure future private investment?

This is addressed in the previous scaling plan section.

What are the relevant lessons for other social enterprises working in this space? Are there plans to disseminate to other stakeholders, if any?

We believe our current results are not yet applicable to other social ventures, but will keep this in mind in the future.

What are your intended next steps in the next 6 months-1 year?

- In June 2015, we will be visiting Malawi and plan to have initial meetings with MOH personnel and PAM personnel in order to garner further interest and further solidify implementation plans.
- Beginning in July 2015, we will be conducting another study using the AutoSyP device for delivering magnesium sulfate to pre-eclamptic women at QECH. The purpose of this study is to validate the use of AutoSyP in delivery fluids to a wider clinical adult population as opposed

to a pediatric population.

- In July 2015, we are planning a stakeholder conference call which will involve personnel from Rice, QECH, MOH, and 3rd Stone Design. In this call we will discuss the details of the plan for scale-up and discuss concerns and interests of all stakeholders. The outcome of this call will be a solidified scale-up plan as well as next steps for any/all stakeholders.

- We are planning to apply for Phase II DIV funding during summer 2015.

- Once funding is secured, we will secure a formal agreement with our manufacturing partner. This will include consulting for design updates as well as production of evaluation units for the scale-up.

- Once funding is secured, we will develop an MOU with the MOH regarding scale-up details, responsibilities, and timeline. At this time, we will also apply for NHSRC regulatory approval for the scale-up (if applicable), and begin meetings with district hospitals.

References

- [1] World Health Organization. Global Health Observatory Data Repository, 2014.
<http://apps.who.int/ghodata/>.
- [2] Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet. 2005;365:891–900.
- [3] March of Dimes, PMNCH, Save the Children, World Health Organization. Born too soon: the global action report on preterm birth. Geneva: WHO, 2012.
- [4] World Health Organization. Global Health Estimates. Available from:
<http://www.who.int/evidence/bod>.
- [5] Becton Dickinson. <https://www.bd.com/globalhealth/>.
- [6] U.S. Food and Drug Administration, Center for Devices and Radiological Health. White Paper: Infusion Pump Improvement Initiative. April 2010.
<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/UCM206189.pdf>.
- [7] Go Medical. Springfusor® Data Sheet.
http://www.gomedical.com.au/products/springfusor_data_sheet.htm.
- [8] World Health Organization. Global Health Observatory Data Repository, 2012.
<http://apps.who.int/gho/data/#>.

Appendix A: AutoSyP User Interface Updates

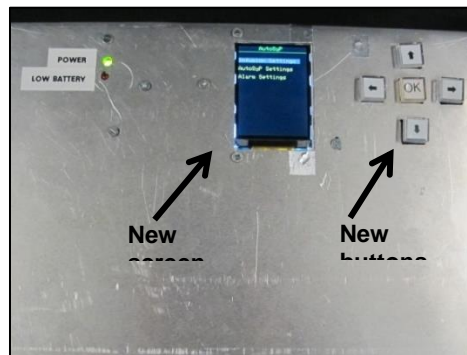
Overview

We received feedback from our clinical partners and from a human factors consultant regarding limitations of our user interface (Fig. A1). The LED interface was limited to displaying only 16 characters at a time, so it greatly limits the information that can be conveyed to the user. This can increase the risk of user error and therefore decrease the safety of the device. Additionally, the buttons were not user-friendly. The following sections will describe the details of the key user interface updates that were made to arrive at our new user interface design (Fig. A2).

Fig. A1: Old User Interface



Fig. A2: New User Interface



Key User Interface Updates

Improved Buttons

The buttons on the old user interface were too thin for a finger to easily press (Fig. A3). The old buttons were also spaced too close to each other, increasing the risk of an unintentional button press. The new buttons have appropriate size and spacing, as well as improved labeling (Fig. A4).

Fig. A3: Old Buttons



Fig. A4: New Buttons



Bigger Screen

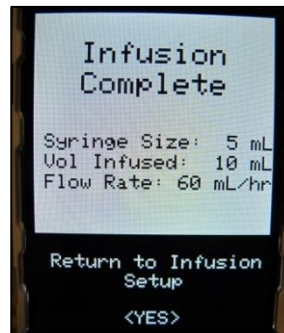
The old screen had a 16-character space limit and an area of 1.4 square inches. The new screen can display >1000 characters and has an area of 2.7 square inches. This allows for much more information to be conveyed at a time. The images below show the information conveyed on the old and new screens when an infusion is complete (Fig. A5 and Fig. A6). The

subsequent sections describe other updates that were able to be made with the larger screen.

Fig. A5: Old Screen



Fig. A6: New Screen



More Information during Alarms

With the new screen, we are able to display more information during an alarm scenario. For example, when an occlusion is detected, we are able to display not only that alarm indication, but also what the user's options for a response are, such as muting the alarm and resuming or permanently quitting the infusion (Fig. A7 & Fig A8). This reduces user confusion during an alarm scenario.

Fig. A7: Old Alarm Screen



Fig. A8: New Alarm Screen

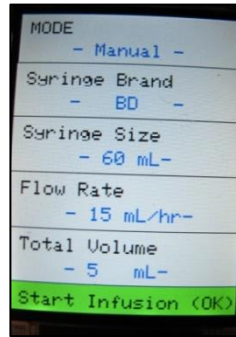


Infusion Settings Programmed on One Screen

In the old screen, the user had to navigate through several screens while setting up an infusion (Fig. A9). This increased risk of incorrectly programming the infusion because the user does not have access to all the settings on the same screen and may forget previous selections. On the new screen, the user can program all of the settings on a single display; therefore, the user sees the previous selections made and can reference/change them without changing the screen (Fig. A10). Before beginning the infusion, the user can easily review all settings that have been made.

Fig. A9: Old Settings Screens

Fig. A10: New Settings Screen



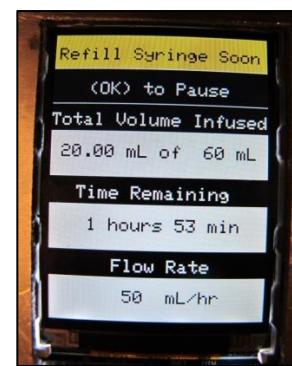
Infusion Information Displayed During Infusion

In the old screen, there was limited information that could be displayed during an active infusion (Fig. A11). With a larger screen, we are able to clearly display the amount of volume that has currently been infused, the time remaining for the infusion, and the programmed flow rate (Fig. A12). In the example below, there is also a caution that indicates that the syringe will need to be refilled soon. There is also a clearer indication of how to pause the infusion.

Fig. A11: Old Infusing Screen



Fig. A12: New Infusing Screen

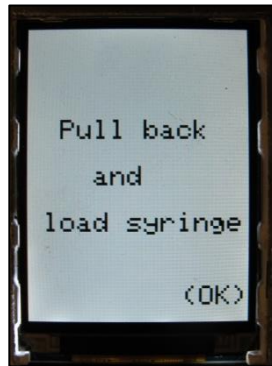


Clear Instructions for Next Steps

The larger screen enables us to give clear instructions to the user regarding buttons to push or next steps to be performed. In the old screen, the user was often expected to “guess” which button would lead to the next screen. An example is shown below, where in the old screen there are no instructions for navigating away from the current screen, but in the new screen the user is instructed to press <OK> (Fig. A13 and Fig. A14).

Fig. A13: Old Reminder Screen

Fig. A14: New Reminder Screen



Multiple Options during Pause

The only option during a pause with the old screen was to resume the protocol (Fig. A15). With the bigger screen, the user can resume the infusion, quit the infusion, or adjust the setup for the infusion (Fig. A16, Fig. A17). Additionally, the screen displays how much volume has been infused so far, the remaining time, and the programmed flow rate. The 'New Pause Screen' (Fig. A16) was originally presented to nurses during the Malawi device trainings. Their feedback was that it was overwhelming because it had too many options to select, so it was simplified to the 'Final Pause Screen' (Fig. A17).

Fig. A15: Old Pause Screen



Fig. A16: New Pause Screen

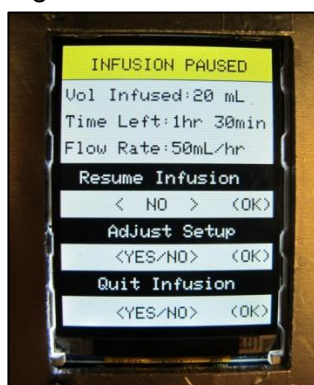
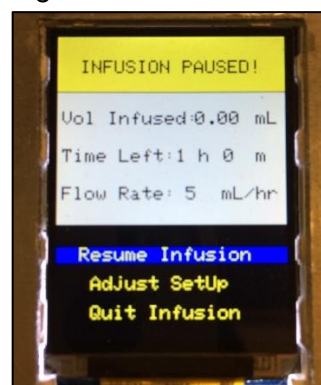


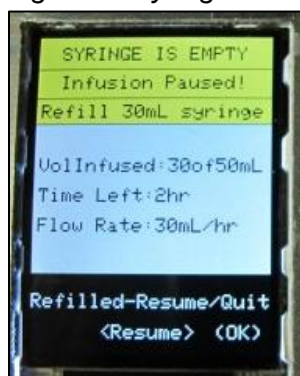
Fig. A17: Final Pause Screen



Clear Instructions for Refilling

The new screen enables us to give clear information and instructions when a syringe is empty but an infusion needs to continue (Fig. A18). There are several amounts of critical information that need to be conveyed at this time, including informing that: 1) syringe is empty, 2) infusion is paused, 3) syringe size that needs to be refilled, 4) volume infused so far, and 5) time left in the infusion. The user also has the option to refill the syringe and continue to protocol or to quit the protocol. These indications and options were simply not possible in the previous 16-character display.

Fig. A18: Syringe Refill Screen



Appendix B: Product Requirements Specification

Revision History

| Revision # | Description | Date | Initials, Org |
|------------|--------------------------------------|------------------|---------------|
| V1 | Initial draft | 31 October 2014 | KRM, Rice 360 |
| V2 | Minor updates throughout document | 11 November 2014 | KRM, Rice 360 |
| V3 | Minor updates based on team feedback | 17 November 2014 | KRM, Rice 360 |

Document Purpose

This document captures all input requirements for the AutoSyP device including clinical usage, performance, manufacturing, marketing and user interaction requirements. The document shall serve as the initial basis for the design, engineering, manufacturing and testing of the AutoSyP system. Subsequent test protocols, manufacturing specifications, and verification documents may reference this document.

Device Overview

The AutoSyP device is used to deliver fluid to a patient through a syringe at a controlled rate. It is an electro-mechanical system that uses a microcontroller, stepper motor, gear system, and a spring to deliver fluid. The device mechanically depresses a syringe plunger which pushes fluid through an administration set into the infusion site on a patient. The device can be used to deliver various fluids to aid in medical care for a patient.

Device Process Description

The AutoSyP device delivers fluids using the following process:

1. A medical professional indicates the desired flow rate, syringe size, and total volume to deliver using the buttons and screen on the user interface.
2. The microcontroller determines the stepper motor rotation rate based on the user's inputs and controls the stepper motor accordingly.
3. The stepper motor rotates at the programmed rate, which initiates a cam/gear rotation system that releases the spring at a periodic rate.
4. As the spring is allowed to compress, its compression translates the depressor cage of the device along a horizontal axis.
5. The depressor cage translation transmits a compressive force onto the syringe's plunger, forcing the fluid out of the syringe and through the tubing into the patient.

Performance Requirements

1. Compatibility: device shall function under the following conditions. Any deviations from standard use instructions or performance within the following ranges of conditions must be clearly indicated in user material and training sessions.
 - a. Syringe size: 5, 10, 20, 30, 60 ml
 - b. Syringe brands: BD, Monoject, Terumo, B. Braun Omnifix, B. Braun Perfusor
 - c. Flow rate: 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 ml/hr

- d. Tubing (extension set) length: 0 to 60 inches
 - e. Tubing diameter: minibore, standard bore
 - f. Catheter length: 25-44 mm
 - g. Catheter diameter: 16G to 24G
 - h. Fluid type: aqueous
 - i. Delivery route: intravenous, enteral
 - j. Delivery mode: volume/time, bolus
 - k. Clinical population: neonatal, pediatric, adult
 - l. Back pressure: -100 to 300 mmHg
 - i. Laboratory back pressure with setup according to IEC 60601-2-24. This back pressure accounts for ranges of back pressure from fluid type, flow rate, delivery route, range of clinical back pressures, clinical population, catheter length and diameter, tubing length and diameter.
2. Flow rate accuracy requirements
- a. Flow rate accuracy measurements should be conducted according to IEC 60601-2-24.
 - b. Mean flow rate: accuracy shall be >95%
 - i. Mean flow rate is defined as the total volume delivered per syringe divided by the total time to deliver the full syringe volume
 - ii. Mean flow rate is compared to the nominal flow rate set by the user
 - c. Instantaneous flow rate: at least 80 % of the nominal volume shall be delivered at an instantaneous flow rate within ± 50 % of the nominal flow rate
 - i. The instantaneous flow rates, Q_i , are determined by the volume of the solution, V_n , delivered by the device during regular time intervals, T_n , with T_n being 1 % of the nominal time for a full syringe volume to be delivered

Safety Requirements

3. Alarms required
- a. Device must present a visual and audio alert and pause the infusion within 1 minute after the pressure in the patient line has exceeded the programmed occlusion threshold.
 - i. At the lowest flow rate and highest programmed occlusion threshold, device must present a visual and audio alert and pause the infusion within 30 minutes after a hard occlusion in the patient line. Higher flow rates and lower occlusion thresholds will result in faster alerts.
 - b. Device must present a visual alert if the mean flow rate accuracy falls below 95% but remains above 90% during an infusion.
 - i. This can exclude the initial setting period, as mean flow rate accuracy is inherently higher during the start of an infusion. Mean flow rate accuracy during the settling period and length of settling period should be indicated in the user manual.
 - c. Device must present a visual and audio alert and pause the infusion if the mean flow rate accuracy falls below 90% during an infusion.

- i. This can exclude the initial setting period, as mean flow rate accuracy is inherently higher during the start of an infusion. Mean flow rate accuracy during the settling period and length of settling period should be indicated in the user manual.
 - d. Device must present a visual and audio alert and pause the infusion if there is a mechanical failure that causes the device to stop functioning properly.
 - e. Device must present a visual alert if the current syringe will be empty in <10 minutes.
 - f. Device must present a visual and audio alert and pause the infusion if the current syringe is empty.
 - g. Device must present a visual alert if the battery power has <1hr remaining during an infusion.
 - h. Device must present a visual and audio alert and pause the infusion if the battery power has <10min remaining during an infusion.
 - i. Device must present a visual and audio alert when an infusion is complete.
4. System shall be designed to withstand accidental spilling of fluid intended for the syringe or tubing
 5. System shall prevent access to electrical components by a finger
 6. System shall require the use of a tool to access internal components
 7. Device enclosure will have no sharp edges
 8. Electrical mains shall be isolated from the housing to prevent accidental shock
 9. Electrical supply wiring shall be insulated to prevent accidental shorting of wiring connecting power supply system
 10. System shall bear necessary instructions and hazard warning labels to advise users in the proper use of the device and to warn against untrained use

Design and Construction Requirements

11. Usability

- a. System shall remind user to wind spring before use and to prime the tubing before use
- b. System shall indicate power state on or off with both light and position of power switch
- c. During an infusion setup, system shall continuously display the user-selected parameters including flow rate, syringe size, syringe brand, and total volume to infuse.
- d. During an active infusion, system shall continuously inform user of volume delivered, time remaining, and flow rate
- e. System shall allow for user to pause an active infusion
 - i. When paused, system shall allow user to adjust infusion settings
 - ii. When paused, system shall allow user to resume or quit the active infusion
- f. Device enclosure should provide an easy place to lift the device using two hands – ideally these would be defined or protruding handles

12. Mechanical and Environmental

- a. Gross dimensions of the device shall not exceed 16 cm x 18 cm x 35 cm
- b. Weight of the device shall not exceed 5 kg
- c. Device enclosure shall prevent access to internal workings of the device
- d. Device shall resist the ingress of dust or water
- e. Device enclosure shall allow tool access to the internal components of the device by a trained technician
- f. System shall operate in temperatures ranging from 2 to 45 degrees C and 0% - 100% relative humidity without interruption to therapy provided
- g. Sustained operation in a high humidity environment shall not lead to condensation in the enclosure in a manner that could jeopardize safety or long term functionality

13. Durability

- a. Device housing shall withstand impact caused by the moving or dropping of another device on to it from a height of up to 50 cm
- b. Device housing shall withstand dropping from 1 meter onto a concrete floor in such a way as to prevent exposure of internal components or breakage of external elements in a manner that creates an additional hazard
- c. System components, including exposed connectors and tubing, shall withstand accidental pulls, bumps, and snags caused by healthcare workers moving between the patient bedside and the device location

14. Electrical

- a. System shall run and charge battery on 100-240V AC wall mains power
- b. System shall be able to operate from battery power for at least 20 hours
- c. System shall be able to connect to mains using various adaptors or connecting cords for various international plug interfaces
- d. System shall have a removable, power cord rated properly for the application

15. Sound and Vibration

- a. System shall operate within a sound threshold of 60 dB measured 1 meter from the device
- b. Any vibration of the device housing shall be isolated from the mounting surface so as to avoid movement of the system during operation
- c. Sustained operation of the device shall not cause any of the syringe/tubing connections to shake loose due to internal vibrations of the device components.

16. Shipping, Transport, and Storage

- a. System shall be suitable for international shipment in standard shipping cartons and packaging materials – no special cases shall be required
- b. System shall withstand routine vibration and impact associated with international express and ocean going shipment

- c. System shall withstand one year of storage in temperatures ranging from 0 degrees C to 65 degrees C within any degradation to performance

17. Cleaning and Sterilization

- a. Device enclosure shall be cleanable via wipe down with sterilizing agents including a 10% diluted bleach and water solution or Cidex
- b. Device enclosure shall have no surfaces which collect dust that are not accessible for wiping down with a paper towel or rag

Documentation and Labeling Requirements

18. Users Manuals

- a. System shall ship with a detailed user manual showing visual explanations of proper set-up, maintenance and storage procedures
- b. Device enclosure shall provide a place for display of an abbreviated user guide that allows for quick reminders and guidance in the set-up of the device for a trained user

19. Labeling

- a. System shall ship with safety labeling in place on the device enclosure
- b. Device enclosure shall bear permanent labeling advising the user of the risks associated with improper use of the device and precautionary steps suggested for set-up
- c. User operable controls shall be labeled in a manner compliant with international standards for medical devices